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(57) Abstract

The present invention relates to a composition for topical application to the skin of a person which composition comprises a dermatologically acceptable carrier medium, characterised in that the carrier medium comprises as essential components at least three ingredients selected from the group consisting of: a) a physiologically acceptable polyalkylene-ether-glycol or alkylene-glycol, or mixtures of such ether glycols and/or glycols; b) a physiologically acceptable C_8-C_{14} aliphatic monohydric alcohol; c) a physiologically acceptable plant extract having antifungal and/or antibacterial properties at physiologically acceptable dosage levels; and d) a physiologically acceptable material having skin moisturising properties. The invention also provides a method for the treatment of the skin or the transdermal application of a medicament which comprises applying a biologically effective amount of a composition of the invention to the skin.

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COMPOSITION FOR TOPICAL APPLICATION

The present invention relates to a composition, notably to a carrier composition for topical application of a wide range of pharmacologically active substances.

BACKGROUND TO THE INVENTION:

Conventional creams or ointments are traditionally designed to deliver an active ingredient only to the epidermal surface of the skin or, at best, to provide limited delivery through the surface skin layers. Most formulations rely on an intimate dispersion or solution of the active ingredient in a suitable oily medium or a water/oil or oil/water emulsion. Thus, a medicament is presented to the epidermal surface in a form likely to penetrate at most only into the outer stratum corneum of the epidermis.

This is considered satisfactory for the treatment of skin conditions where surface involvement is the only consideration, e.g. for infective conditions where repair processes can occur within the skin layers when the surface insult has been removed by a topical treatment.

For deeper/underlying disease states or where it is desired to use the skin as a route for the delivery of drugs to the systemic circulation, different formulation concepts or the use of penetration enhancers are required (see for example "Percutaneous Absorption" Eds R.L. Bronaugh & H.I. Maibach, Marcel Dekker N.Y.) for a discussion of these precepts.

The skin is the largest organ of the body, and it has become of interest as a route of presenting drugs for the treatment of disease states other than those of the skin. A number of benefits may be claimed for the transdermal route over oral or parenteral routes for the application of medicaments. For example, the variability of the so-called first pass effect

following oral administration of many drugs is avoided. The transdermal route is non-invasive as compared to parenteral presentations. However, the transdermal route suffers from a number of disadvantages. For example, it requires the use of a carrier for the medicament which can pass through the skin, since the stratum corneum presents a profound barrier to the passage of a wide range of materials, offering great resistance to most medicaments.

Therefore, the transdermal route has usually been considered suitable only for relatively potent (low dose) medicaments. Furthermore, great care needs to be exercised to ensure that components in the carrier composition do not cause skin irritation or damage.

We have now devised a carrier composition containing a synergistic mixture of ingredients which enables a surprisingly high rate of transdermal transport of the medicament to be achieved, thus reducing the above problems. The composition of the invention makes it possible to apply medicaments by the transdermal route which had hitherto been considered unsuitable for use in such an application route.

It has also been proposed in US Patent No 4560553 to use eucalyptol as a means for enhancing the skin penetration of biologically active materials, including methotrexate. Eucalyptol is an essential oil within the meaning of the term as used herein. However, in that proposal, the eucalyptol was stated to be the ingredient responsible for the transdermal properties of the compositions described therein and therefore must be present in such compositions. We have found that the synergistic properties of the mixture of the ingredients of our compositions enables the essential oil to be omitted and this is contrary to the requirements of the US proposal.

SUMMARY OF THE INVENTION:

Accordingly, the present invention provides a composition suitable for the topical application of a medicament, which composition comprises a dermatologically acceptable carrier medium, characterised in that the carrier medium comprises as essential components at least three ingredients selected from the group consisting of:

a. a physiologically acceptable polyalkylene-ether-glycol, notably one of the empirical formula $HO-(C_nH_{2n}O)_m-OH$, where n has an average value of from 2 to 6 and m has an average value of from 2 to 30 or more, in which the alkylene groups can be straight or branched chain, saturated or unsaturated, and in which the hydroxyl groups can be primary, secondary and/or tertiary, and/or a physiologically acceptable alkylene-glycol, notably one of the empirical formula $HO-(C_pH_{2p})_q-OH$, where p has a value of from 2 to 6 and q has an average value of from 1 to 30, in which the alkylene groups can be straight or branched, saturated or unsaturated, and the hydroxyl groups can be primary, secondary and/or tertiary; or mixtures of such polyalkylene ether glycols and/or alkylene glycols;

b. a physiologically acceptable C_8-C_{14} aliphatic monohydric alcohol, notably a C_{9-12} alcohol, for example lauryl or dodecyl alcohol, which latter may be derived from propylene tetramer;

c. a physiologically acceptable plant extract having anti-fungal and/or anti-bacterial properties at physiologically acceptable dosage levels, for example an essential oil, notably one containing a terpenoid compound, preferably an oxygen-containing terpene or mixture of such terpenes, for example as is present in tea tree oil and other essential oils derived from vegetable matter; and

d. a physiologically acceptable material having skin moisturising properties.

We have found that the ingredients of the composition of the invention interact synergistically to achieve a greater than expected transdermal effect and that this effect is achieved

when three of the specified ingredients are present in the composition. However, it is preferred that the composition contains all four of the essential ingredients, optionally in admixture with other ingredients typically present in topical preparations; and preferably also contains a medicament which is to be administered transdermally. Typically, the medicament is present in from 0.1 to 10%, the ether glycol and/or glycol ingredient a is present in a total amount of from 0.25 to 30%, the essential oil ingredient c is present in from 0.1 to 10%, the alcohol ingredient b is present in from 0.5 to 10%, and the skin moisturiser ingredient d is present in from 0.1 to 5%, all percentages being by weight of the active ingredient based on the total composition, the remainder of the composition typically being water or a water based gel or matrix having the medicament and essential ingredients uniformly distributed throughout.

The carrier compositions of the invention exhibit both transdermal and intradermal properties and thus find use in the topical application of compositions where minor systemic properties are required and in the transdermal application of active compositions which are to be active systemically. The composition thus finds use in the application of salves and other medicaments to the skin to treat physical and other damage to the skin, for example open wounds or cuts, abrasions, ulcers or burns. Since many of the essential oils which can be used as ingredient c exhibit preservative as well as anti-bacterial properties, compositions containing such essential oils may be self preserving and assist the prevention of infection in open wounds or abrasions due to these properties of the essential oil ingredient.

The compositions find especial application in the transport of a wide range of medicaments through intact stratum corneum. For example, the medicament may be selected from one or more of: anaesthetics, analgesics, anti-inflammatory agents, anti-cancer agents, cardiovascular agents, anti-fungal, anti-

bacterial, anti-viral, anti-proliferative, anti-emetic drugs and hormones. Specific examples of suitable medicaments include benzocaine, lidocaine, tetracaine as local anaesthetics; ibuprofen, ketoprofen, indomethacin, diclofenac, piroxicam as anti-inflammatory agents or mild analgesics; fentanyl, buprenorphine and morphine as strong opiate analgesics; clotrimazole, miconazole, ketoconazole, amphotericin and griseofulvin as anti-fungal agents; nifedipine, nicardipine, timolol and atenolol as cardiovascular agents; methotrexate (and its analogues) or 5-fluorouracil as anti-proliferatives or cytotoxics; allantoin as an enhancer of skin repair regrowth; benzoyl peroxide or anti-biotics of the tetracycline, penicillin or cephalosporin type; anti-emetics such as metaclopramide, buclizine and cyclizine; steroids such as hydrocortisone, progesterone, oestradiol and dexamethasone; hormones such as melatonin and thyroxine; and tranquillisers and sedatives of the phenothiazine or butyrophenone type.

From another aspect, the present invention provides a method for the topical treatment of the skin of a mammal and/or for the application of a medicament transdermally to a mammal, characterised in that it comprises applying a biologically effective amount of a composition of the invention to the skin.

The invention is applicable to a wide range of medicaments as described above. The invention may also be applied to precursors of the active medicaments, for example an acetate or acyl derivative, an alkali metal salt or an amine salt or complex thereof.

For convenience, the term medicament will be used herein to denote in general terms a active ingredient of a medicament, its analogues and precursors thereof, whether alone or in admixture with one another.

As indicated above, the composition of the invention finds widespread use in the treatment of a wide range of conditions

for which the medicaments have been indicated, eg. in the application of methotrexate in the treatment of proliferative skin disorders including: psoriasis; primary malignant disease, for example squamous cell carcinoma, basal cell carcinoma, malignant melanoma, Kaposis sarcoma etc.; and secondary deposits in the skin and neoplasms due to or associated with warts, herpes simplex, human papilloma virus etc..

We have surprisingly found that, in laboratory in vitro transdermal experiments using isolated human stratum corneum preparations, the skin penetration properties of medicaments contained in carrier compositions containing at least three, and preferably all four, of the specified essential ingredients are generally superior to the rates obtained with formulations which use other ingredients, for example Azone, as a penetration assistant, or formulations which do not contain at least three of the specified essential ingredients. The invention thus offers the ability to apply medicaments transdermally in effective amounts and also to use lower concentrations, for example from 0.1 to 2%, of the medicament, which is of advantage where large areas of the skin are to be treated. However, where localised application of the medicament is required, for example in the treatment of a small skin cancer, higher proportions, for example from 5 to 10% by weight, may be used if desired and acceptable.

The carrier composition may contain customary ingredients used in such compositions. However, we have found that the carrier composition must contain at least three of the specified ingredients in order to obtain the enhanced penetration of the medicament through the skin. The order of preference for the specified ingredients to be present is:

1. the plant extract ingredient c;
2. the skin moisturising material ingredient d;
3. the long chain alcohol ingredient b; and
4. the alkylene glycol or polyalkylene ether glycol ingredient a.

The polyalkylene ether glycols or alkylene glycols for present use as ingredient a typically have a molecular weight in the range 100 to 600,000, but are preferably those having a molecular weight in the range 200 to 6000. We have found that such ether glycols and glycols provide the carrier with occlusive properties as well as providing solvent and transdermal properties. Their inclusion in the carrier composition is especially preferred when the medicament is to be applied over a prolonged period where drying out of the skin could occur. The ehter glycols and glycols also assist formation of a matrix within which the other components of the composition are dispersed to provide a stable viscous gel consistency to the composition. Where the ehter glycol or glycol has a short chain, for example 2 to 5 carbon atoms, the ether glycol or glycol may also serve as a solvent or co-solvent for other components of the composition.

The polyalkylene ether glycols and/or alkylene glycols are typically present in a total amount up to about 30% by weight of the total composition, preferably 1 to 25%, and mixtures of glycols and ether glycols may be used.

The long chain alcohol ingredient b is preferably a straight chain aliphatic alcohol containing from 9 to 12 carbon atoms, or the analogous branched chain alcohols obtained by condensation of propylene. The alcohol serves as a lubrifacient to aid direct application of the composition to the skin and also assists transdermal penetration of the medicament. The presence of the long chain alcohol is therefore preferred when the composition would otherwise be excessively viscous and is particularly desirable when the polyalkylene ether glycol or alkylene glycol is also present.

The long chain alcohol ingredient b is present in an amount of up to about 30%, for example from 1 to 25%, preferably 1 to 10%, of the total composition.

The plant extract ingredient c can be selected from a wide range of such material which exhibit anti-fungal and/or anti-bacterial properties. Preferably, the plant extract also exhibits preservative properties at dosage rates of the ingredient which are physiologically acceptable. That is, the plant extract exhibits physiologically useful effects at a dosage rate similar to the rate at which the other ingredients are applied to the skin in the composition. Thus, the amount of the plant extract required to achieve useful effects does not imbalance the overall composition.

Preferably, the plant extract is an essential oil as defined at page 670 of Martindale, The Extra Pharmacopoeia, 28th edition. Such essential oils include those derived from the foliage of plants and trees and are typified as containing terpenoid compounds. These may be hydrocarbon terpenes or oxygen containing compounds, for example terpene alcohols, ketones or oxides. Specific preferred terpene compounds include a-pinene, a-terpinene, limonene, 1,8-cineol, gamma-terpinene, p-cymene, 1-terpinen-4-ol, aromadendrene, a-terpineol, and mixtures thereof. The terpene compounds for present use may be synthetic or naturally occurring, as when a eucalyptus type tree oil is used, notably the oil from Melaleuca alternifolia tree, known as Tea Tree Oil.

The plant extract ingredient c may thus be used as the naturally occurring mixture of materials containing the active ingredient, or may be used in the form of an isolated and refined extract containing a raised proportion of the active ingredient or as an individual synthetically prepared single compound or mixture of isomers.

The plant extract ingredient c is typically present in up to 15%, for example from 0.1 to 10%, preferably 0.5 to 5%, notably from 0.5 to 2.5%, by weight of active ingredient based on the total composition and serves primarily as a penetration assistant in the composition. It is therefore preferred that

such a plant extract be present as one of the specified ingredients in any composition according to the invention.

The skin moisturising agent for use as ingredient d is a compound or mixture of compounds which maintains or increases the hydration of the stratum corneum of the skin. A number of materials are known to possess this property and specific examples include: urea; lactic, ascorbic or glycollic acids and salts thereof; cholesterol; liposomes and niosomes; pyrrolidone carboxylic acid and salts thereof; gamma-linoleic acid and its salts; mono- and poly-aminosaccharides; chitins and chemically modified chitins which contain ether and extra alkyl groups; and hyaluronic acid. Mixtures of such skin moisturising agents may be used if desired.

The skin moisturising agent ingredient d is present in an amount of up to about 10%, for example from 0.1 to 5%, preferably from 0.1 to 2% by weight of the total composition.

As stated above, the composition may contain other ingredients normally present in topically applied compositions. Typically these will provide up to 50%, for example from 0.1 to 35% by weight of the total composition. Such other ingredients include for example solvents or co-solvents, such as water, low molecular weight alcohols, eg. ethyl or propyl alcohols or glycols; and penetration enhancers, such as long chain acids, esters, glycols or saccharide derivatives. The presence of long chain fatty acids and derivatives, notably esters, thereof is especially preferred since they aid formation of stable gels when all four of the specified ingredients are present. Particularly preferred fatty acids and esters thereof for present use are those of the empirical formula Alk-OOCAcid where Alk denotes a straight or branched alkyl group containing from 2 to 18 carbon atoms and Acid denotes a saturated or unsaturated straight or branched chain alkyl group which may carry one or more Alk-OOC- substituents. Typical of such fatty acid esters are C_1 to C_{18} alkyl esters of octanoic acid or

octanoic acid itself.

Other ingredients which may also be present include, for example, a pH controlling agent such as sodium, potassium, ammonium or an alkaline-earth metal hydroxide, or an organic base of the primary, secondary or tertiary amine type, to give a final pH in the range 4.5 - 9.0 and more preferably 7.0 - 8.5.

The ingredients c are often obtained from natural materials and will therefore differ in composition and be a mixture of the desired ingredient with other materials. Such mixtures may be used without the need to isolate the specified ingredient and the percentages given above are in terms of the desired component of such mixtures, Where the mixture contains large amounts of physiologically acceptable other components, these may themselves provide beneficial other properties, for example fragrance to the composition, and it may be necessary to use larger amounts of the mixture to achieve the desired proportion of the desired essential oil component than the percentages given above. The percentages should therefore be treated as guides to the desired amounts and the optimal amounts can be readily determined by simple tests.

The compositions of the invention can be prepared using a wide range of techniques, for example by admixing and stirring together the desired amounts of the various ingredients to form a cream, paste or gel. If desired, the ingredients can be pre-dissolved or suspended in one or more of the other ingredients, for example in a propylene glycol solvent, to aid formation of a stable gel or emulsion. In some cases it may be desirable to subject the composition at some stage during its preparation to high speed shear working taking care to avoid entrainment of air, notably where a resin thickener or cellulose derivative is used as a gelling agent. Where necessary, the pH of the composition can be adjusted by the addition of a suitable pH regulator after the other ingredients have been incorporated.

The compositions of the invention are applied to the affected areas of the skin of a mammal, notably a human being, to treat the wound, psoriasis or other skin damage or disorder by applying the composition as a coating over the affected area or can be applied to any desired area where the medicament is to be absorbed into the body for a systemic effect elsewhere in the body, for example in the treatment of hypertension etc. This can be achieved by applying the composition directly in the required amount as a cream, paste or gel to the skin, for example by wiping a gel stick type presentation of the composition which exposes a desired length of stick across the desired area of the skin until the exposed portion of the stick has been applied to the skin. Alternatively, the composition can be put up in a pressurised dispenser formulation and applied as a spray, foam, mousse or gel via a metered dose valve, which dose can then be spread over and/or massaged into the skin. Alternatively, the composition can be applied to an adhesive plaster, pad, gauze or other backing support member or carrier which is then applied over the affected area. The coating of the composition on the skin or on the support member can have applied thereto a vapour barrier film, for example a plastic film or a spray on film-forming resin, for example a synthetic skin type composition, which serves to retain water and other fluids in the composition and the skin. However, where the polyalkylene ether glycol or alkylene glycol ingredient a is present in sufficient amounts, this may provide a gel matrix for the other components and also impart sufficient occlusive properties for the use of a vapour barrier membrane not to be necessary.

The amount of the composition applied will be sufficient to apply the biologically effective amount of the active ingredient(s) therein to the affected area of the skin or to achieve the desired dosage application. This amount will vary according to the treatment required and the content of active ingredient in the composition. The optimal amount required to achieve the desired biological effect can readily be

established as is known from a knowledge of these.

DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION:

The following examples are provided for illustration only and are not intended or designed to limit the scope of the invention. All parts and proportions are given by metric weight and volume units unless stated otherwise.

Example 1

A co-solution of stearic acid (8 parts by weight) and propylene glycol (8 parts by weight) was prepared at 70°C with mechanical stirring. A separate solution of a mixture of polyethylene glycol (ingredient a, average molecular weight 400, 6 parts by weight) in polyethylene glycol (ingredient a, average molecular weight 4000, 20 parts by weight) was prepared similarly. The two solutions were mixed together at 60-65°C using a mixer without entrainment of air. A solution of sodium hydroxide (1.12 parts), a polyaminosaccharide condensate skin moisturising agent (ingredient d, 1.1 parts by weight) in deionised water (25 parts by volume) was slowly added with stirring. The mixture was slowly cooled to 30°C with high shear mixing without entrainment of air to give a viscous white pasty mass. The mass was mixed with a solution of Tea Tree oil (ingredient c, 1 part by volume), dodecanol (ingredient b, 2 parts by weight) and, as a lubrifacient to aid preparation of the mixture and application of the composition to the skin, an emollient ester of polypropylene glycol and myristic acid (0.2 parts by weight) in ethanol (24 parts by volume). The mixture was stirred continuously for one hour to give a creamy hydrogel base and packed into a sealed container until used (Formulation II, FII). Similar hydrogel base compositions were made but with varying ingredients as set out below:

Formulation I: FII, dodecanol ingredient b omitted

Formulation III: FII, cetyl alcohol replaces dodecanol

Formulation IV: FII, moisturising agent ingredient d omitted

Formulation V:	FII, methyl cellulose (5 parts) in place of polyethylene glycol ingredient a
Formulation VI:	FII, emollient and moisturising agent ingredients d replaced with a saccharide ester emollient
Formulation VII:	FII, omitting the essential oil ingredient c

Methotrexate of BP grade was mechanically admixed in varying amounts (1% w/w, 0.5% w/w, 0.25% w/w, 0.2% w/w and 0.1% w/w) with the hydrogel bases and the resultant compositions stored in sealed, light-tight containers until used.

The compositions were applied as a coating of about 0.05 to 0.1 grams per square cm to samples of isolated human stratum corneum (obtained from mammary reduction or abdomenoplasty for several different donors) prepared as described by Skerrow & Skerrow (1985) or Kligman & Christophers (Arch.Dermatol. 88 702 (1974).

Transdermal delivery was measured in micrograms per square centimetre per hour using a stability indicating hplc assay method, sampling the stirred receptor layer over periods up to 96 hours. The cells (made of glass) were similar to those described by Franz (Curr. Probl. Dermatol.7-58 (1978). The compositions were applied to the epidermal surface of the stratum corneum and the dermal side was bathed by a stirred phosphate buffered saline solution containing 10% ethanol. The system was maintained at 32°C, light was excluded and the exposed surface of the applied composition was occluded to prevent alcohol and water loss. Two or more cells were run for each formulation and the skin integrity was assessed visually both before and after the experiment using a hand lens.

The results for these tests are set out below:

Table 1 - donor 2

1% w/w MTX	72 hr release rate of MTX in microgram/cm^2/hour
Formulation I	1.0
II	5.5
III	1.0
IV	0.1
V	None detected
VI	0.6
VII	0.7

Table 2 - donor 2

0.25 and 0.5% MTX		72 hour release rate
Formulation II	0.25%	5.0
II	0.5%	4.5
IIa	0.5%	5.8

Formulation IIa = formulation II with addition of 1 part of a silicone wetting agent - dimethicone CS20.

Table 3 - using Formulation II, varying amounts of MTX:

	Cumulative amount of MTX released in mcg/cm^2		
0.2% MTX	24hr	48hr	72hr
Donor 1	8.9	17.2	28.2
Donor 2	85.7	289	407
Donor 3	10.0	88.5	--
Donor 4	10.0	--	--
0.1% MTX	24hr	48hr	72hr
Donor 4	14.7	--	--
0.5% MTX	24hr	48hr	72hr
Donor 4	17.2	--	--

1.0% MTX	24hr	48hr	72hr
Donor 4	33.4	--	--

For Formulation II containing all four specified ingredients, significant penetration of methotrexate (MTX) occurred at 24, 48 and 72 hours when compared to results obtained by previous workers (see for example K R Brain et al, Int. J. Pharm. vol 71 R9, 1991 where only 200 nanograms per square centimetre per 24 hours, and approximately 600 nanograms at 48 hours, were achieved).

When formulations in which one of the specified ingredients had been omitted were used, the above results show that lower, but still useful penetration of the MTX was achieved.

Example 2:
Attempts were made to prepare a composition containing only two of the four specified ingredients required for the formulations of the invention. In all cases the products were unacceptable as being unstable or as being too thick and could not easily be incorporated into formulations for applications to the skin. No useful results could be obtained from such compositions due to the impossibility of applying them effectively to the skin.

Example 3:
Formulations corresponding to Formulation II of Example 1 were prepared using a range of different medicaments. These were tested as in Example 1 and the following cumulative amounts of the medicament were transferred over the stated periods:

heparin:	1.5 to 2.2 IUs/cm^2 over 72 hours
fenclofenac:	263 mcg/cm^2 over 24 hours
piroxicam:	109 mcg/cm^2 over 24 hours
metoclopramide:	10.5 mcg/cm^2 over 24 hours
vincristine:	2.0 mcg/cm^2 over 24 hours
	2.8 mcg/cm^2 over 48 hours

CLAIMS:

1. A composition suitable for the topical application of a medicament, which composition comprises a dermatologically acceptable carrier medium, characterised in that the carrier medium comprises as essential components at least three ingredients selected from the group consisting of:

a. a physiologically acceptable polyalkylene-ether-glycol and/or an alkylene-glycol, or mixtures of such glycols and/or ether glycols;

b. a physiologically acceptable C_8-C_{14} aliphatic monohydric alcohol;

c. a physiologically acceptable plant extract having anti-fungal and/or anti-bacterial properties at physiologically acceptable dosage levels; and

d. a physiologically acceptable material having skin moisturising properties.

2. A composition as claimed in claim 1, characterised in that the polyalkylene-ether-glycol has the empirical formula $HO-(C_nH_{2n}O)_m-OH$, where n has an average value of from 2 to 6 and m has an average value of from 2 to 30, in which the alkylene groups can be straight or branched chain, saturated or unsaturated, and in which the hydroxyl groups can be primary, secondary and/or tertiary.

3. A composition as claimed in either of claims 1 or 2, characterised in that the alkylene-glycol has the empirical formula $HO-(C_pH_{2p})_q-OH$, where p has a value of from 2 to 6 and q has and average value of from 1 to 30, in which the alkylene groups can be straight or branched, saturated or unsaturated, and the hydroxyl groups can be primary, secondary and/or tertiary.

4. A composition as claimed in either of claims 2 or 3, characterised in that the ether glycol and/or glycol has an average molecular weight in the range 200 to 6000.

5. A composition as claimed in any one of the preceding claims, characterised in that the monohydric alkanol is a C_{9-12} alcohol.

6. A composition as claimed in claim 5, characterised in that the alkanol is lauryl or dodecyl alcohol or a propylene tetramer alkanol.

7. A composition as claimed in any one of the preceding claims, characterised in that the plant extract ingredient c is an essential oil containing a terpenoid compound.

8. A composition as claimed in claim 7, characterised in that the terpenoid compound is an oxygen-containing terpene or mixture of such terpenes.

9. A composition as claimed in any one of the preceding claims, characterised in that the skin moisturising agent ingredient d is selected from urea, lactic, ascorbic or glycollic acids and salts thereof, cholesterol, liposomes and niosomes, pyrrolidone carboxylic acid and salts thereof, gamma linoleic acid and its salts, mono- and poly-aminosaccharides, chitins and chemically modified chitins which contain ether and extra alkyl groups, and hyaluronic acid; and mixtures containing such agents.

10. A composition as claimed in any one of the preceding claims, characterised in that it contains all four of the essential ingredients.

11. A composition as claimed in any one of the preceding claims, characterised in that it also contains a medicament.

12. A composition as claimed in claim 11, characterised in that the medicament is methotrexate.

13. A composition as claimed in claim 1, characterised in that

it contains a medicament in from 0.1 to 10%, the ether glycol and/or glycol ingredient a is present in a total amount of from 0.25 to 30%, the plant extract ingredient c is present in from 0.1 to 10%, the alcohol ingredient b is present in from 0.5 to 10%, and the skin moisturiser ingredient d is present in from 0.1 to 5%, all percentages being by weight of the active ingredient based on the total composition.

14. A composition as claimed in claim 13, characterised in that the substantially all of the remainder of the composition is provided by water or a water based gel or matrix having the ingredients uniformly distributed throughout.

15. A support member for application to the skin of a mammal, characterised in that a composition as claimed in any one of the preceding claims is provided on the support member.

16. A method for the topical treatment of the skin and/or for the application of a medicament transdermally, characterised in that it comprises applying a biologically effective amount of a composition as claimed in any one of the preceding claims, or a support member carrying such a composition, to the skin.

17. A method as claimed in claim 16, characterised in that the composition is a composition as claimed in claim 13.

18. A method for making a composition as claimed in claim 1, characterised in that the desired ingredients are admixed or stirred together in the desired proportions.

19. A composition according to claim 1 substantially as hereinbefore described.

AMENDED CLAIMS
[received by the International Bureau on 24 March 1993 (24.03.93);
original claims unchanged; new claims 20-23 added (1 page)]

20. A composition suitable for the topical application of a medicament, which composition comprises a dermatologically acceptable carrier medium, characterised in that the carrier medium comprises a total of at least 50% by weight thereof of at least three essential ingredients selected from the group consisting of:

a. a physiologically acceptable polyalkylene-ether-glycol and/or an alkylene-glycol, or mixtures of such glycols and/or ether glycols;

b. a physiologically acceptable C_8-C_{14} aliphatic monohydric alcohol;

c. a physiologically acceptable plant extract having anti-fungal and/or anti-bacterial properties at physiologically acceptable dosage levels; and

d. a physiologically acceptable material having skin moisturising properties.

21. A composition as claimed in claim 1, characterised in that the composition also contains a total of from 0.1 to 35% by weight of the total composition of a carrier, solvent or co-solvent for the composition selected from water or a low molecular weight alcohol or glycol.

22. A composition as claimed in claim 1, characterised in that it also contains a total of from 0.1 to 35% by weight of the total composition of a long chain fatty acid or ester thereof of the empirical formula Alk-OOCAcid where Alk denotes a straight or branched alkyl group containing from 2 to 18 carbon atoms and Acid denotes a saturated or unsaturated straight or branched chain alkyl group which may carry one or more Alk-OOC- substituents.

23. A composition as claimed in claim 22, characterised in that the acid is octanoic acid and the ester is a C_{10} to C_{18} alkyl ester of octanoic acid.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01950

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K47/10; A61K47/44; A61K47/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	US,A,4 797 402 (DORSEY) 10 January 1989 see the whole document	1-4,7-9, 11,16, 18-19
X	GB,A,496 893 (R.E. GOLDSBROUGH) 5 January 1939 see the whole document	1,7-9
A	GB,A,1 001 949 (F. MEYER) 18 October 1965 see the whole document	1-19
A	EP,A,0 069 385 (MERCK & CO.) 12 January 1983 see the whole document	1-19

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 JANUARY 1993	25. 01. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HOFF P.J.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201950 SA 65804

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 05/01/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4797402	10-01-89	None	
GB-A-496893		None	
GB-A-1001949		DE-B- 1227616	
		FR-A- 1329357	
		NL-A- 281225	
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		JP-A- 58015910	29-01-83
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